DETAILED ACTION

Response to Amendment

1. In the amendment filed 06/07/2011, Applicant cancelled claims 1-4 and 7, amedned claims 5-6 and 8-10 and added the new claims 12-14. Claims 5-6 and 8-14 are pending and currently examined.

Priority

2. Since the verified English translation of JP 2003-384863 was submitted to the Office, the foreign priority is recognized as 11/04/2003. However, as Applicant is very well aware, the effective filling date has not changed from the filling date of the PCT/JP/2004/016761, 11/11/2004 (see MPEP 706.02).

Withdrawn claim rejections

3. The rejection of claims 5-11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

4. The rejection of claims 5-7 under 35 U.S.C. 102(b) as being anticipated by Endou et al. (CA 2456172- published 04/03/2003- cited in the previous Office action) is withdrawn in view of the amendments to the claims.

5. The double patenting rejection of claims 5-7 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Pat. No. 7,510,847 is withdrawn in view of the amendments to the claims.

Maintained and new claim rejections necessitated by amendment

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 5-6 and 8-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, it is not clear, in the independent claims 5, 8, 10 and 14, how the uric uptake **into** the cell can be at the same time elimination of the uric acid **into** the cell. Therefore, the metes and bounds of the claims could not be determined.

8. Claim5-6 and 8-14 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: performing the method on either a control cell or with a control substance and comparing the results in order to be able to identify the compound as useful.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 5, 8-11, 12 and 14 remain and are, respectively, rejected under 35 U.S.C. 103(a) as being unpatentable over Endou et al. (CA 2456172- published 04/03/2003- cited by Applicant) in view of Kanellis et al. (Uric Acid Stimulates Monocyte Chemoattractant Protein-1 Production in Vascular Smooth Muscle Cells Via Mitogen-Activated Protein Kinase and Cyclooxygenase-2, Hypertension, 41, 1287-1293, 2003) and Hurteau et al. (Transforming growth factor beta inhibits proliferation of human ovarian cancer cells obtained from ascites, Cancer, 74, 93-99, 1994).

The claims are drawn to methods of screening a substance efficacious for healing, preventing or treating vascular disorders, hypertension, and renal disorders, the methods comprising using a cell line expressing URAT1 in the presence or absence of a test compound; and assaying the proliferation ability of the cells or the amount of a monocyte chemotactic factor (MCP-1) produced by the cells. The proliferation ability of the cells is assayed by measuring the thymidine uptake level by the cells.

Endou et al. teach a novel urate transporter gene participating in the urate transport in the kidney and a urate transporter which is a polypeptide encoded by the above gene (abstract). The protein product is named URAT1 and has the same amino acid sequence as the protein used in the instant Application. Furthermore, Endou et al. provides a screening method of a substance having modulatory action for the uric acid transport. The URAT1 works for transporting uric acid into the cells and is deeply involved in the reabsorption of the uric acid. Also, as is shown in Figures 6, 8, 9 and 10, it is possible to quantify the accelerating or inhibiting action for uric acid uptake of the screening substance in the system where the URAT1 is expressed, by adding uric acid

to the system, further adding the screening substance thereto, and comparing a uric acid uptake amount with that in the case with no addition of the screening substance. As is shown in Figures 6 and 8, the substances clinically used as uricosuric accelerators have remarkably inhibited the uptake of uric acid in the above experimental system, and thus, it is shown that it become possible to screen the uricosuric accelerating action of the screening substance in this system. As the cells used in this screening system, the cells are not limited to oocytes used in the experiments, and it is possible to use various living cells as long as the cells can express URAT1. The modulators identified can regulate the uptake of uric acid by the urate transporter involved in the urate transport in the kidney, and therefore can be used as an active ingredient of the medicines for the treatment/prevention of various diseases associated with the reabsorption of uric acid such as hyperuricemia and gout. It is possible to make the obtained active ingredient a pharmaceutical composition using a pharmacologically acceptable carrier (p.10-11). This may be used in humans, where hyperuricemia becomes a risk factor for cardiovascular diseases and hypertension (p.1).

Although Endou et al. teach that the method of screening may be performed using various living cells as long as the cells can express URAT1, they do not mention specifically vascular smooth muscle cells or HUVEC. They are also silent of assaying the proliferation of the cells in the screening process by thymidine incorporation as well as about the quantitation of MCP-1 in response to the screening process.

Kanellis et al. teach that soluble uric acid can induce vascular smooth muscle cells proliferation, activated through ERK, MAPK Cox-2 or PDGF pathways

(introduction). Also taught is that uric acid increases the production of MCP-1 protein in rat VSMC (p.1289, left col., last paragraph). The teachings of Kanellis et al. underscore the pathogenic role of uric acid in hypertension, vascular disease and atherosclerosis (p. 1292, left col. third paragraph).

Hurteau et al. exemplify a well-known and routinely use of thymidine incorporation assay for determining cell proliferation (abstract and Material and methods).

Since the uric acid, in order to exert its effects, necessarily has to be transported in the cells by a transporting mechanism and, in view of Endou et al., this is through URAT1, identifying modulators of URAT1 can, in view of Hurteau et al and Kanellis et al. be performed by proliferation assays in VSMC or by detection of MCP-1.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to employ the teachings of Hurteau et al. and Kanellis et al. in the methods of Endou et al. with a reasonable expectation of success, because the assays were routinely used in the art and Kanellis et al. showed the usefulness of employing VSMC in finding modulators in uric acid pathogenesis.

On page 8 of the Remarks Applicant argues that, by submitting a verified translation of the Japanese priority document which was filed on November 14, 2003 (less than 1 year from the publication date of Endou et al.) the Endou et al. document (CA2456172) may not properly be applied against the present application under 35 USC §102(b). The arguments were carefully considered but not found persuasive

because as Applicant is surely aware of, the effective date of the instant Application remains the filing date of PCT/JP/2004/016761, 11/11/2004. However, the argument against the rejection application under 35 USC §102(b) is moot in view of the cancelation of the rejection as a consequence of the amendments to the claims.

With regard to the Application of the Endou et al. as a reference for a rejection under 35 USC 103(a), as presented *supra*, the reference is valid to be used as a prior art reference.

On page 9 of the Remarks Applicant argues that Kanellis and Hurteau do not cure the alleged deficiencies of Endou et al. The arguments were carefully considered but not found persuasive because as presented above, the Kanellis et al document based their work on vascular smooth muscle cells.

On page 10 of the Remarks Applicant argues that no reasonable expectation that one of ordinary skill in the art could treat vascular disorders not induced by hyperuricemia. The arguments were carefully considered but not found persuasive because, first of all, this is a new limitation introduced with the new claims. Second, the method claimed is a screening method and not a treatment method. The intended use of the compounds detected in the screening method is not linked and does not limit the claims and does not have affect the patentability of the Application.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 5 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 7,510,847 in view of Kanellis et al. (Uric Acid Stimulates Monocyte Chemoattractant Protein-1 Production in

Vascular Smooth Muscle Cells Via Mitogen-Activated Protein Kinase and Cyclooxygenase-2, Hypertension, 41, 1287-1293, 2003- cited previously). The transporter used in the method of screening of the patent is the same and the method has the same outcome as in the instant Application. Even though the patent does not mention Vascular smooth muscle cells, Kanellis et al. teach that soluble uric acid can induce vascular smooth muscle cells proliferation, activated through ERK, MAPK Cox-2 or PDGF pathways (introduction). Also taught is that uric acid increases the production of MCP-1 protein in rat VSMC (p.1289, left col., last paragraph). The teachings of Kanellis et al. underscore the pathogenic role of uric acid in hypertension, vascular disease and atherosclerosis (p. 1292, left col. third paragraph). Thus, it would have been obvious to performed the method claimed in the '847 patent on Vascular smooth muscle cells as taught by Kanellis et al. with a reasonable expectation of success , because the assays were routinely used in the art and Kanellis et al. showed the usefulness of employing VSMC in finding modulators in uric acid pathogenesis.

Conclusion

13. No claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 9:00-18:30 M-Th and 9:00-18:30 alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Elly-Gerald Stoica/
Primary Examiner, Art Unit 1647